Attorney Docket No. O/99469 US

**REMARKS**

Upon entry of the above amendment claims 1, 3-11 and 13-16 will be pending in the instant application. Claim 13 has been withdrawn due to a restriction requirement. Applicants have amended the claims to better reflect what Applicants consider their invention. The amendments are clerical in nature and do not narrow the claims in any manner.

***Priority***

Applicants acknowledge that the Examiner has reported that **SOME** of the certified copies of the priority documents have been received in the January 15, 2002 Office Action. Applicants respectfully request the Examiner to identify what copies are present in the file and what copies are not present.

*Issue Under 35 U.S.C. §102(b)*

Claims 1, 3, and 4 stand rejected under 35 U.S.C. §102(b) as being anticipated AN-CA62:1704c, HCAOLD and AN-CA61:4426h, CAOLD (abstract of BE 623844). Applicants submit the patentable distinctions between the cited prior art and the present invention.

Distinctions Between the Present Invention and AN-CA62:1704c and AN-CA61:4426h

The Examiner has identified the compound of registry number 95171-22-5 as being a specific example of interest from the Chemical Abstract reference. The Chemical Abstract reference is an abstract of Belgian Patent No. 623844 (Smith '844). Applicants attained Smith '844 and submitted it with the response of April 15, 2002. The compound in the Chemical Abstract is based on a mistake made the transcriber at Chemical Abstracts. Therefore, the Chemical Abstract reference does not have enabling the disclosure and the compound referenced has not been made in Smith '844.

Smith '844 discloses 17-substituted steroids without a substituent on position 7. While Smith '844 is in French, a skilled artisan would recognize that on page 2, the structural names fail to disclose a steroid with substitution at the 7 position. Applicants submit that for the compound cited in the abstract and by the Examiner, the Chemical Abstract transcriber apparently dropped off the digit 1 before the 7; thus changing the compound from a 17 substituted steroid to a 7 substituted steroid.

Thus, the formula disclosed in the Chemical Abstract is based only on an erroneous name and the underlying reference,

Smith '844, fails to provide an enabling disclosure for 7-substituted steroid as set forth in the present invention.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." Verdegaal Bros. v. Union Oil Co. of California, 814 F.2d 628, 631, 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987). Clearly, Smith '844 fails to disclose each and every element of the present invention as set forth in the claims.

Applicants respectfully request withdrawal of the 35 U.S.C. §102(b) rejection.

*Issue Under 35 U.S.C. §112*

Claims 1, and 7-11 stand rejected under 35 U.S.C. §112, second paragraph as being indefinite. The Examiner asserts that claim 7 claims a compound that is disclaimed in claim 1, which causes confusion.

Applicants have addressed this issue by canceling claim 7. Applicants respectfully request withdrawal of the 35 U.S.C. §112, second paragraph.

*Issue Under 35 U.S.C. §103(a)*

Claims 1, 3-11 and 14-16 stand rejected under 35 U.S.C. §103(a) as being obvious over Bardin '834 (USP 5,342,834). Applicants respectfully submit that patentable distinction exist between the present invention and the cited prior art.

Distinctions Between the Present Invention and Bardin '834

The Examiner asserts that Bardin '834 discloses similar compounds (7α-methyl), whereas the claimed compounds are ($C_2$-$C_3$) alkyl. The Examiner then points out column 7, lines 9-14 of Bardin '834 as providing motivation to modify Bardin '834.

Bardin '834 discloses a method of providing androgen supplementation without inducing an abnormal weight gain in the prostrate. *See column 1, lines 11-13.* More specifically, Bardin '834 discloses that "a particular group of androgens is not metabolized to their 5α-reduced form in the prostrate and other tissues. Thus administration of these compounds-testosterone derivatives with a non-hydrogen substituent in the 6α or 7α-position - allows one to provide androgen supplementation therapy without stimulating abnormal prostrate growth." *See column 2, lines 12-20.* Bardin '834 fails to disclose the unexpected effect of superior oral activity. Bardin '834 fails to even address oral activity of the

compounds. Bardin '834 only discloses intramuscular, subcutaneous or transdermal administration. See claim 8.

Applicants emphasize that the present invention provides orally active androgens. Bardin '834 fails to provide motivation to a skilled artisan to modify the disclosure of Bardin '834 to make the present invention as described in the present claims.

Applicants respectfully request withdrawal of the 35 U.S.C. §103(a) rejection.

*Unexpected Results*

If the Examiner is still not persuaded that a *prima facie* case of obviousness has not been established, Applicants resubmit the attached 37 C.F.R. §1.132 Declaration by Dr. M.E. De Gooijer, which was previously submitted on December 2, 2002.

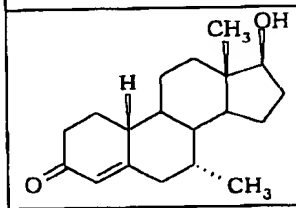
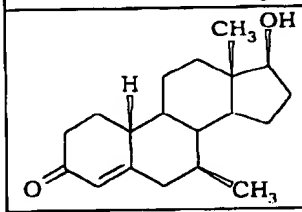
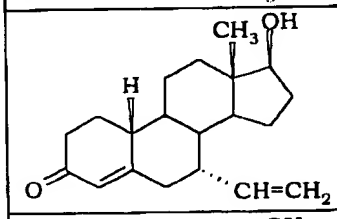
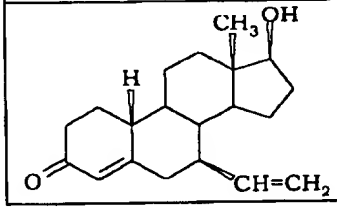
Regarding Bardin '834

The submitted data show that a change in the stereochemistry at the 7 position imparts an unexpected change in the oral activity effect of the compounds in this field. Inspecting the comparison of MENT with 7β-methyl nandrolone or 7α-vinyl nandrolone with 7β-vinyl nandrolone (Table 1), one can

see the major improvement in androgen receptor activation by selecting the 7α stereoconfiguration.

**Table 1**

**A**: Androgen receptor activity (data from declaration)

| Compound structure | Compound name | A |
|---|---|---|
|  | 7α-methyl nandrolone; 7α-methyl-19-nortestosterone; MENT | 269% |
|  | 7β-methyl nandrolone | 14% |
|  | 7α-vinyl nandrolone | 190% |
|  | 7β-vinyl nandrolone | 8% |

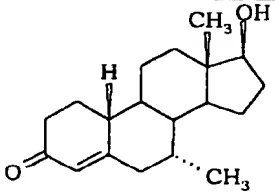
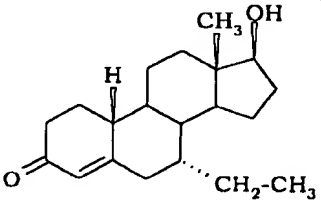
On top of this, the invention discloses the importance of selection of a substituent length of more than one carbon atom

at position 7 of the nandrolone skeleton. This skeleton is also named 19-nortestosterone or 17β-hydroxy-estr-4-en-3-one.

The effect is illustrated by comparison of MENT with 7α-ethyl-nandrolone (Table 2). This is also done in the patent specification on page 25 and 26, wherein Example 1 is 7α-ethyl-nandrolone. Although some activity is lost in the in vitro androgen receptor assay, there is higher activity by oral administration.

**Table 2**

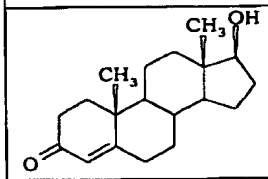
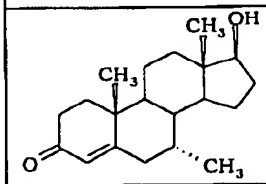
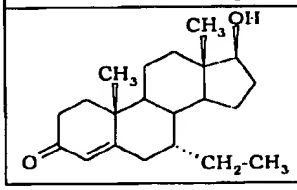
**A**: Androgen receptor activity (data from declaration)
**B**: Metabolic stability $t_{1/2}$ (min) with human hepatocytes (data from specification)
**C**: $ED_{50}$ in mg/kg p.o. in LH suppression assay (data from specification)

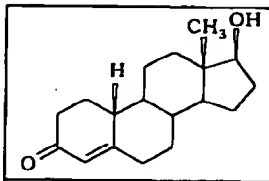
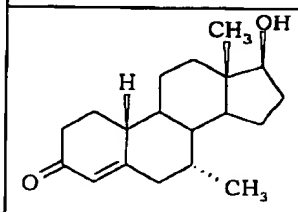
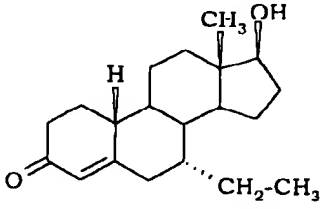
| Compound structure | Compound name | *Measurement results* | | |
|---|---|---|---|---|
| | | *A* | *B* | *C* |
|  | 7α-methyl nandrolone; MENT; 7α-methyl-19-nortestosterone | 269% | 20 min | 10 |
|  | 7α-ethyl-nandrolone (7α-ethyl, 17β-hydroxy estr-4-en-3-one) | 152% | 48 min | 2.5 |

Applicants assert that it is well known that testosterone steroids have different activity than 19-nortestosterone (nandrolone) analogs. Thus, a skilled artisan would have no basis for comparison between the testosterone analogs and the 19-nortestosterone. Thus, the superior results shown in Table 3 and the accompanying §132 declaration would be unexpected to a skilled artisan.

**Table 3**

**A**: Androgen receptor activity (data from declaration)
**B**: Metabolic stability $t_{1/2}$ (min) with human hepatocytes (data from specification supplemented with data from declaration)
**C**: $ED_{50}$ in mg/kg p.o. in LH suppression assay (data from specification)

| Compound structure | Compound name | *Measurement results* | | |
|---|---|---|---|---|
| | | **A** | *B* | *C* |
|  | testosterone | 16.5% | 15 min | |
|  | 7α-methyl-testosterone | 45% | | |
|  | 7α-ethyl-testosterone; Compound 2 in Solo et al | No in house data available | | |

| | | | | |
|---|---|---|---|---|
|  | nandrolone (19-nortestosterone | 55% | 16 min | |
|  | 7α-methyl nandrolone; MENT; 7α-methyl-19-nortestosterone | 269% | 20 min | 10 |
|  | 7α-ethyl-nandrolone (7α-ethyl, 17β-hydroxy estr-4-en-3-one) | 152% | 48 min | 2.5 |

Applicants respectfully submit that the unexpected activity is in reference to oral activity. Applicants respectfully request withdrawal of both 35 U.S.C. §103(a) rejection in light of the unexpected results discussed above and in the attached §132 declaration.

*Conclusion*

Applicants submit that every issue raised by the outstanding Office Action has been addressed and rebutted. Therefore, the present claims define patentable subject matter and are in condition for allowance.

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Should the Examiner believe that a conference would be helpful in advancing the prosecution of this application, he is invited to telephone Applicants' Attorney at the number below.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2334 for any additional fees required under 37 C.F.R. §§ 1.16 or 1.17; particularly, extension of time fees.

Respectfully submitted,

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Attorney Docket No. O/99469 US
MWM

Enclosure: 37 C.F.R. §132 Declaration